Noncyanotic Congenital Heart Disease

Introduction

This lesson and the one that follows it (Plumbing #5: *Cyanotic Congenital Heart Disease*) catalog the common or high-yield congenital heart defects, all of them a failure of embryogenesis. These defects can be cataloged in multiple ways. We've chosen to catalog them based on patient presentation—what you will actually see if you care for pregnant women or children. Thus, as stated in the lesson titles, we have divided congenital heart defects into noncyanotic and cyanotic. The noncyanotic congenital heart defects have no cyanosis at presentation. No cyanosis means that these defects will present with a **pink baby with a murmur**. These all represent **simple defects—**although they may small or large, these defects are usually just a hole or connection between the chambers of the two hearts of our two-heart model. Because blood flows through the path of least resistance and the left heart is far stronger than the right heart, these conditions are **left to right shunts**. Oxygenated blood from the left ventricle goes to the systemic vasculature, perfusing tissues as it should, AND goes into the right ventricle, into the pulmonary arteries.

All congenital problems—cyanotic and noncyanotic—come down either to a failure of the mesoderm-derived **myocardium to form** or the neuroectoderm-derived **neural crest cells to migrate**. Neural crest migration is covered in Neuroscience. For now, think of neural crest cells as highly versatile cells that travel all over the embryo, forming the peripheral nervous system, all of the autonomics in all organs (including the heart), and the key structures that separate chambers—the aorticopulmonary septum and endocardial cushion. You will see the aorticopulmonary septum and endocardial cushion in the next lesson as well. You are responsible for the mechanisms as well as the diagnoses in the Basic Sciences, but try to keep them categorized as noncyanotic and cyanotic, not as neural crest and myocardium.

Noncyanotic Congenital Heart Defects in General

If there is ever an opening between the two hearts, the **left heart wins**. The left heart wins because it is designed to beat against (and during embryogenesis, had been beating against) the high systemic pressures of the aorta and systemic vasculature. The right ventricle is designed to beat against the much-lower-resistance pulmonary vasculature. Because there is a hole between the two hearts, it is theoretically possible for the right heart to send deoxygenated blood out through the defect. That doesn't happen because the left heart is so much stronger, and the pressure in the aorta is so much higher. To make matters worse, the pulmonary artery is the path of least resistance. The size of the defect is what limits how much blood flows to the pulmonary artery because the defect's radius determines the resistance to blood flow from the left ventricle.

That means that noncyanotic heart defects have more flow through the pulmonary arteries, resulting in **increased pulmonary vascular markings** on X-ray early in the disease. Noncyanotic heart defects present as **pink babies with a murmur** on the first day of life. If not corrected, however, the right ventricle gets used to the increased pressure (more on this next paragraph). Ventricles respond to excess afterload by undergoing concentric hypertrophy. Thus, **right ventricular hypertrophy** may be seen on X-ray, ECG, or echocardiogram. The gold standard for diagnosing a noncyanotic heart defect is an **echocardiogram**. The noncyanotic congenital heart defects are abbreviated with three letters, and they all have a D in them (as compared to the cyanotic congenital heart defects, which all have a T in them): ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA). Correction can be surgical or sometimes medical, but almost all of them should be closed.

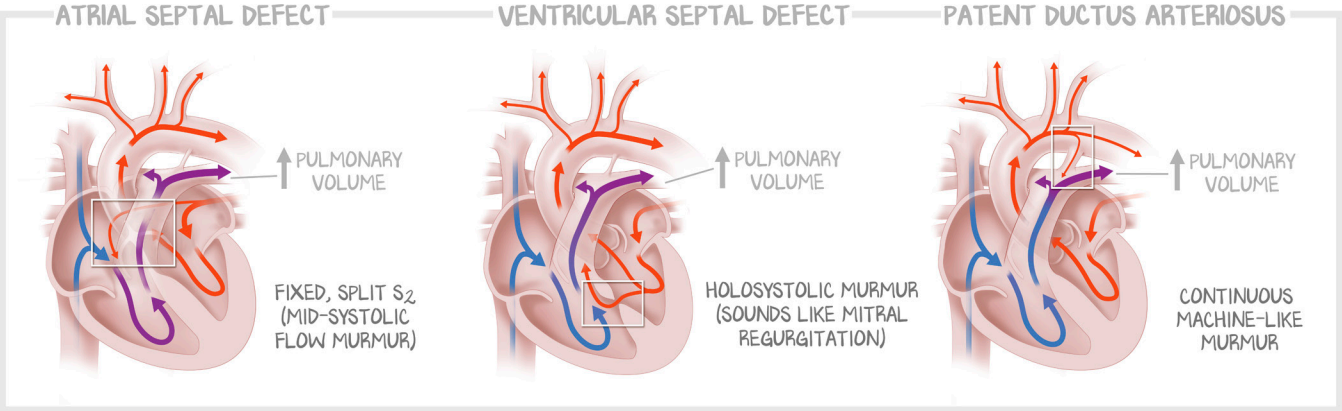

Figure 4.1: Overview
This introductory illustration shows the anatomical defects and the murmur associated with each lesion. Notice how all three show a purple arrow in the pulmonary artery, representing the mixing of oxygenated and deoxygenated blood. Oxygenated blood still reaches the periphery, and deoxygenated blood still returns from the periphery. The red-blue mixing only happens in the right atrium, left atrium, or ductus arteriosus.

The long-term consequence of failing to repair a left-to-right shunt is **Eisenmenger syndrome**, the eponym for **reversal of the shunt**. Regardless of how the connection from left to right is made, an increased volume is delivered to the pulmonary artery, and with it, increased pressure. The tissues tell the arterioles how much pressure they need (*hyperemia*), and the arterioles have their set point. As the pulmonary arterioles receive more volume and pressure from the left ventricle, they are stretched out. Being stretched, they contract back (myogenic response). Because each heartbeat carries excess volume and pressure, the pulmonary arterioles have a sustained response to contract back (myogenic response). Sustained contraction results in **smooth muscle proliferation—**the tunica media enlarges. Vasoconstriction results in increased pulmonary vascular resistance—increased afterload to the right ventricle. The right ventricle responds the only way it knows how: **right ventricle** (concentric) **hypertrophy**. It gets stronger and delivers more pressure to the pulmonary arterioles, which see more pressure and contract back. And the cycle continues. The result is **pulmonary hypertension** and **right ventricle hypertrophy**.

The right ventricle is no longer weaker than the left ventricle, and the pulmonary vascular resistance is not so much lower than the systemic vascular resistance, so the right ventricle pushes the blood from right to left. The path of least resistance is no longer through the pulmonary artery but through the aorta. The right ventricle has hypertrophied so much that it can push against the systemic circulation. So finally, after years of abuse from the left ventricle, the right ventricle starts sending **deoxygenated blood** through the hole into the left ventricle and out into systemic circulation. Eisenmenger syndrome is a combination of pulmonary hypertension, right ventricular hypertrophy, and hypoxemia. Hypoxemia manifests as **digital clubbing**, **polycythemia** (excess hemoglobin due to excess EPO production, discussed in Renal and Heme/Onc), and **cyanosis** (blue discoloration of the skin). This reversal only happens after years (diagnosed in adulthood), and only if the defect is not corrected.

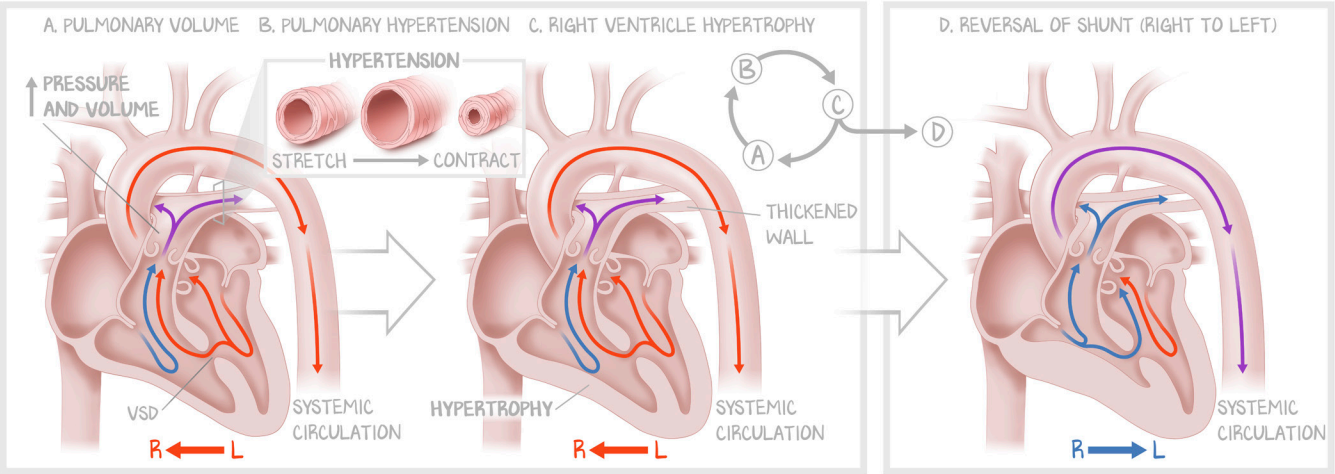

Figure 4.2: Left-to-Right Shunts
(a) A left-to-right shunt enables oxygenated, high-pressure blood from the left ventricle through the septum into the pulmonary artery. Most of the time, this does not compromise systemic perfusion (unless the defect is extremely large). Over time, in response to being stretched out, the arterioles learn to resist the left ventricle by getting stronger. The increased pulmonary arterial pressure combined with the aortic pressure that the right ventricle receives causes the right ventricle to hypertrophy, enabling more blood to go through the pulmonary artery, stretching the arterioles, which contract back. This cycle continues for years until the right ventricle is strong enough and the pulmonary arterial pressure high enough that there is a reversal of the shunt, and deoxygenated blood is sent through the lesion. Ventricular hypertrophy and pulmonary hypertension are irreversible.

Specific Noncyanotic Congenital Defect #1: Atrial Septal Defects

We are starting with the most complicated of the septal defects and working our way toward the simplest. This is done intentionally to give you a sense of ever-improving discomfort. This stuff isn't hard, but making it more than a table to memorize is challenging. Always follow along with the illustrations as you read through the text. We gave you complete views of the septum primum (its growth and apoptosis) and septum secundum in Plumbing #1: *Embryogenesis and Fetal Flow*. We instructed our illustrators to remove what was necessary to see the pathologies. Figure 4.3 has the anterior of all four chambers removed so that you can visualize the relative locations of the septa and ostia. Because the septa grow from the back forward, and we've removed the anterior, you don't see the entirety of the septa as the processes are unfolding. You do get a final look at the atrial septum as if you are standing to the right of the heart, peering through the right atrium.

An **atrial septal defect** (ASD) is a hole between the two atria and the **most common congenital defect after the first year of life** (see VSD for reasoning). These defects are usually small, do not compromise the hemodynamics, and can't cause Eisenmenger syndrome on their own (the right ventricle doesn't send blood back through the tricuspid into the right atrium and across into the left atrium), although pulmonary hypertension and right ventricular concentric hypertrophy may occur. Baby will be pink with a murmur. The murmur you are listening for is a **fixed split S_2**. S_2 is made by the closure of the semilunar valves. With an ASD, the right ventricle is delivered slightly more blood than the left. Increased preload, increased stroke volume. The right heart has a larger stroke volume and sends a larger volume into the pulmonary arteries than the left ventricle sends into systemic circulation because some of the right ventricle's cardiac output (which returns to the left atrium) is returned to the right ventricle through the ASD. Because there is more blood in the right ventricle than the left, on every beat, the pulmonic valve stays open a little longer than the aortic valve, generating two discrete sounds that are constant beat to beat.

The right atrium sees an increased volume, so it changes the only way it knows how—dilation, eccentric hypertrophy. However, the excess preload to the ventricle is rarely sufficient to induce right ventricular dilation. The right atrial dilation compromises the electrical pacemakers of the heart—the SA node and AV node—leading to arrhythmias, such as atrial fibrillation and atrial flutter.

The naming convention for ASDs is unfortunate. There is a septum primum, ostium primum, septum secundum, ostium secundum, primum type ASD, and secundum type ASD. Septums and primums all over the place, but only the **ostia line up.** The ostium primum is related to the septum primum's growth, the ostium primum getting smaller and smaller as the septum primum grows. The ostium secundum is a result of the septum primum's apoptosis. The septum secundum is responsible for zero kinds of ASDs. Only the foramen ovale (next section) has anything to do with the septum secundum. So instead, when you read or say an ASD type, say all these words, every time: "*ostium primum ASD, neural crest*" for primum type ASDs and *"ostium secundum ASD, exaggerated apoptosis"* for secundum type ASDs.

A **primum type ASD** ("*ostium primum ASD, neural crest*") is a persistent hole left behind caused by the **failure of neural crest migration** from the endocardial cushion to the septum primum. Failure of neural crest migration accounts for only 10% of ASDs. The ostium primum is the space not yet traversed by the septum primum as it grows toward the endocardial cushion. We simplify this course by being binary, so for your studying, learn that primum type ASD is ALWAYS an endocardial cushion defect (knowing that the growth of the septum primum could also technically be the cause). The location of the primum type ASD is **near the endocardial cushion.**

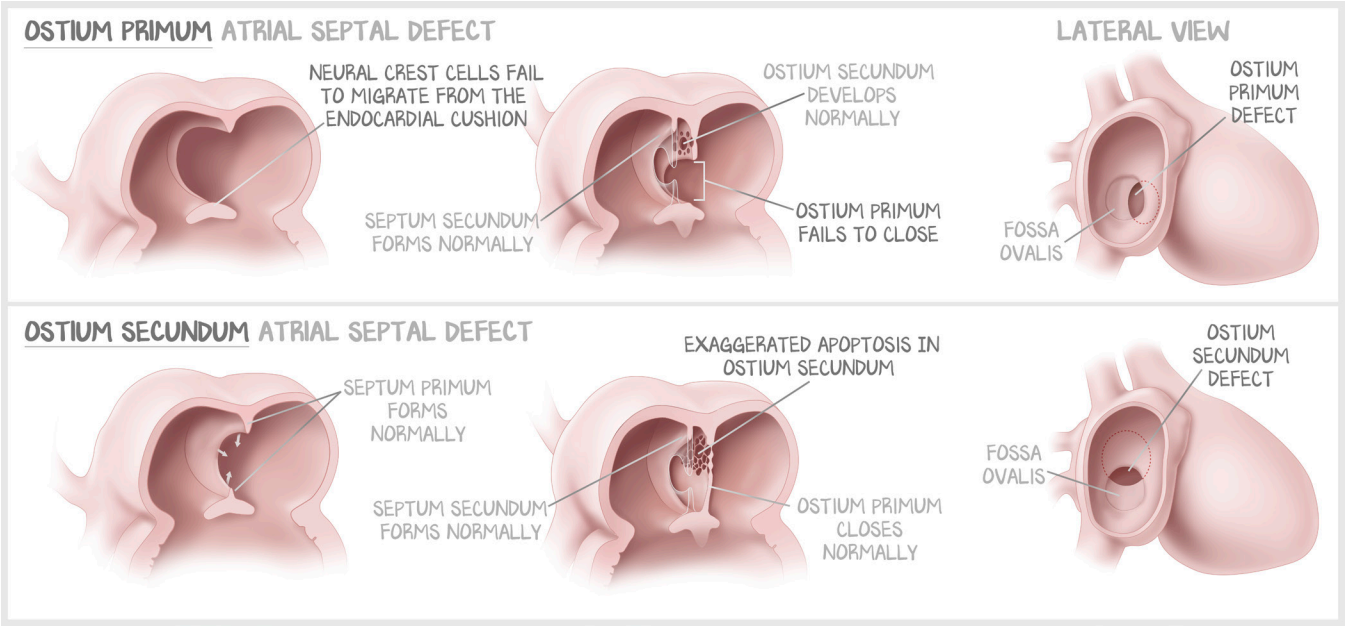

Figure 4.3: Atrial Septal Defects
In an ostium primum atrial septal defect, the neural crest cells fail to migrate from the endocardial cushion. The ostium secundum forms normally, as does the septum secundum. From the lateral view, the failure of the neural crest cells to migrate makes the defect near the endocardial cushion. In the ostium secundum atrial septal defect, there is an overproliferation of the septum primum, resulting in a large defect—a larger ostium secundum.

A **secundum type ASD** (*"ostium secundum ASD, exaggerated apoptosis"*) is caused by a persistent hole made by the **ostium secundum** and is an exaggerated response of apoptosis. That is to say, the septum primum did everything correctly and joined with the endocardial cushion. It is supposed to undergo apoptosis to form the ostium secundum. If the septum primum overdoes it, and the hole is too large, the septum secundum won't grow far enough to occlude the hole.

A Patent Foramen Ovale Is Not an ASD

A patent foramen ovale is a potential hole between the two atria. A patent foramen ovale is found in 25% of patients, almost always clinically silent, and is not considered to be a congenital defect. The foramen ovale is the gap left by the septum secundum in the posterior inferior portion of the atria. This spot on the septum primum does not undergo apoptosis to become the ostium secundum. The flap of tissue that is left behind enables blood from the right atrium to push the flap open as the blood from the lower extremities bypasses the right ventricle. Upon birth, the lungs open, and low-resistance vessels drop the resistance in the pulmonary vasculature. At the same time, the higher pressure in the right atrium causes the flap to close against the septum secundum, and the two should fuse.

A patent foramen ovale is not open but rather **openable**. The failure to fuse with the septum primum means that if there is a surge in pressure from the right atrium, the added pressure could open the patent foramen ovale and eject blood or blood contents into the left atrium. This comes up on licensure exams under the presentation of a **paradoxical embolism**. Thrombosis of the deep veins of the legs breaks free and travels to the heart. There are no valves in large veins. That clot should go to the right atrium, then the right ventricle and pulmonary artery, finally becoming lodged in the pulmonary vasculature—a **pulmonary embolism**. If a patient has a deep vein thrombosis, that clot shouldn't be able to embolize to the systemic vasculature. The only way it can is to travel up the IVC (which is targeted at the foramen ovale). The clot opens the foreman ovale and enters the left atrium. An extremely rare event that does not warrant surgical intervention, but something that comes up on licensure exams all the time.

See PFO as a flap problem and ASDs as permanent holes.

Specific Noncyanotic Congenital Defect #2: Ventricular Septal Defects

Ventricular septal defects (VSDs) are holes between the two ventricles. They rarely occur in isolation and are more often associated with a more significant diagnosis. In that case, the VSD "goes along for the ride," where the symptomatology is more severe for the associated condition. VSDs are the most common congenital defects **at birth**. The discrepancy between the prevalence of VSDs (most common at birth) and ASDs (most common after 1 year of age) is because VSDs are either **so small they fix themselves** (so are not present in adulthood) or **so big the baby dies** (or must be closed surgically, preventing death—but not present in adulthood either way). Small defects cause loud murmurs; large defects cause heart failure and failure to thrive. The **murmur** of VSD is **holosystolic**, sounding just like mitral regurgitation. Both mitral regurgitation and VSD involve the left ventricle contracting and sending blood through a hole inappropriately; it's just that mitral regurgitation sends blood into the left atrium, whereas VSD sends blood into the right ventricle.

You can give baby **up to 1 year if the hole is small** to see if it will close spontaneously. If it is **large** or presents with **heart failure** or **failure to thrive**, then **surgical closure** is required.

A **ventricular septal defect** is a hole between the two ventricles caused by a defect in **ventricular septation**. Fewer than 10% of VSDs occur due to defects in the muscular interventricular septum (the mesoderm), and 90% of VSDs occur due to failure of the **membranous interventricular septum**, caused by the **failure of neural crest cell migration**. That form of VSD is, therefore, an endocardial cushion defect. If the membranous part does not grow all the way down, there is an opening between the ventricles **near the endocardial cushion**. The degree of neural crest migration failure determines the severity of disease.

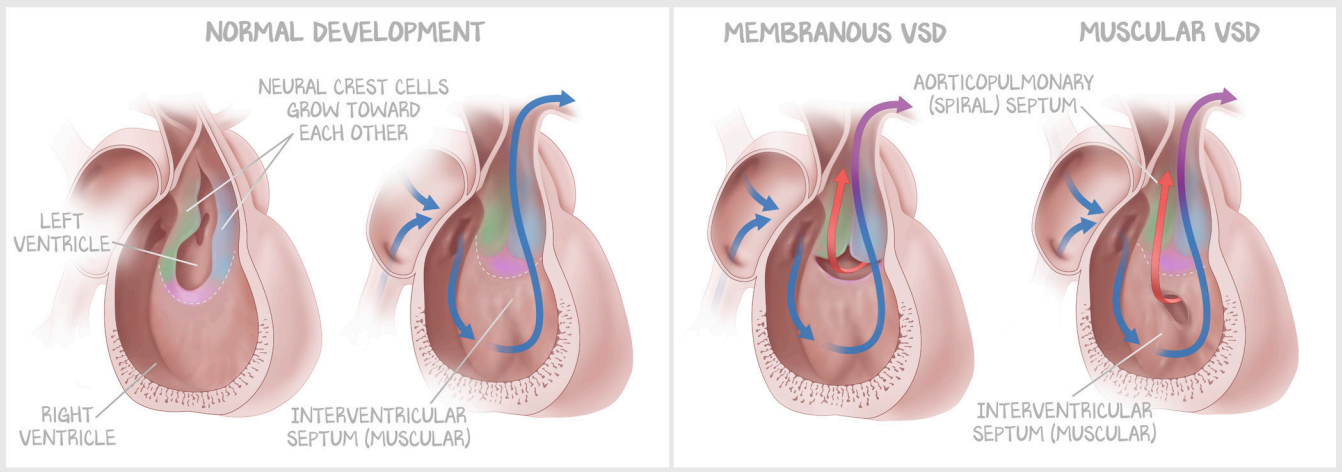

Figure 4.4: Ventricular Septal Defects
The normal development of the interventricular septum involves both the growth of mesoderm to form the muscular interventricular septum (from the base up toward the endocardial cushion) and the fusion of the neural crest cells of the aorticopulmonary septum and endocardial cushion. In a membranous VSD (near the endocardial cushion, caused by a failure of neural crest cell migration), the defect is near the ventricular outflow tract. In a muscular VSD (not near the endocardial cushion, caused by a failure of mesodermal proliferation), the defect is not near the outflow tract.

The migration of the neural crest forms the aorticopulmonary septum, intermembranous ventricular septum, and terminal portion of the atrial septum. Therefore, VSD can present with the failure of any combination of those events, all of which involve some degree of neural crest migration. In the next lesson, we'll see the failure of neural crest migration as the root of the three main cyanotic diseases. All of them present with [something catastrophic] AND a VSD. Endocardial cushion defects are associated with **trisomy 21** (Down syndrome) and **fetal alcohol syndrome**. Don't be tricked. It isn't that either of these cause VSD, ASD, and tetralogy of Fallot; rather, these cause a failure of neural crest migration resulting in VSD, ASD, and tetralogy of Fallot.

Persistent Ductus Arteriosus

The ductus arteriosus is the shunt in fetal circulation that delivers low-oxygen blood from the right ventricle to the aorta after the branching of the vessels to the head and arms. It bypasses the fetal-high-resistance-pulmonary-vasculature, pushing blood from the right ventricle into the aorta. As soon as baby takes its first breath, the vascular resistance of the pulmonary vasculature drops, and the right ventricle then pushes against the very low-resistance pulmonary vasculature, sending deoxygenated blood into the lungs to be oxygenated. The left ventricle then pushes the oxygenated blood, with lots of force, into the aorta and ductus. The passage of left-ventricle blood with **high oxygen concentration** through the ductus signals smooth muscle contraction in the ductus, massively increasing its resistance, closing it. Within days, the ductus scars into the ligamentum arteriosum.

Increasing oxygen concentration through the ductus arteriosus leads to a **decrease in prostaglandins**, which disinhibits myofibroblast proliferation and induces myofibroblast vasoconstriction. Review resources love to cite congenital rubella as the main association. Given the low prevalence of rubella, that isn't the association we want you to make. It is the absence of increasing oxygen levels in the blood going through the ductus arteriosus that prevents its closure. The ductus requires oxygen to initiate closure. The neonates at the highest risk of **hypoxemia** are those whose lungs don't exchange gas well yet, and in whom there is insufficient surfactant to keep their alveoli from closing. The single largest risk factor for that exact condition is **premature delivery**.

In **systole**, the left ventricle pushes oxygenated blood not only into the aorta and systemic vasculature but also **through the ductus** into the pulmonary vasculature. In **diastole**, because the ductus is well after the aortic valve, the elastic recoil of the aorta pushes oxygenated blood **through the ductus**. Oxygenated blood to the periphery, pink baby. This blood flow through the ductus in both systole and diastole gives the characteristic **continuous machine-like murmur** that is classic for this disease.

We can facilitate closure by giving nonsteroidal anti-inflammatory drugs (NSAIDs). **NSAIDs close the ductus** (such as indomethacin, recalled by "endomethacin" which ends the ductus) by inhibiting the production of endogenous prostaglandins, and **prostaglandins keep it open** (prostacyclin E) by artificially keeping the prostaglandin levels high. Maintaining a patent ductus, as we will see in the next lesson on cyanotic congenital defects, is necessary to ensure that some cyanotic disease patients survive until surgery.

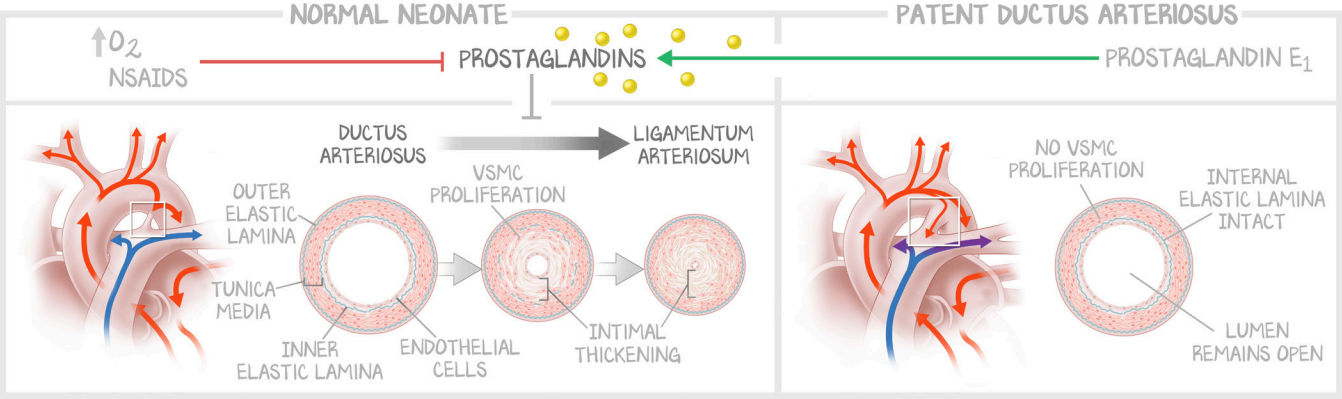

Figure 4.5: Patent Ductus Arteriosus
In a normal neonate, high oxygen tension in the ductus arteriosus induces the inhibition of prostaglandins. This is the proliferation signal for the cells of the tunica media to proliferate into the intima, where they act as fibroblasts, laying down scar tissue (collagen) and contracting the ductus arteriosus, closing it off. In a patient with a patent ductus, that process doesn't happen. Oxygen and NSAIDs close the ductus, infusion of a prostaglandin E_2 analog keeps it open. You will see intimal thickening, the proliferation of the myofibroblasts of the tunica media in idiopathic pulmonary hypertension, in Pulmonary. There, many treatments with the prostaglandin I_2 (called prostacyclin) is the mainstay of treatment. Both are prostaglandins, and both act to prevent vascular smooth muscle proliferation.

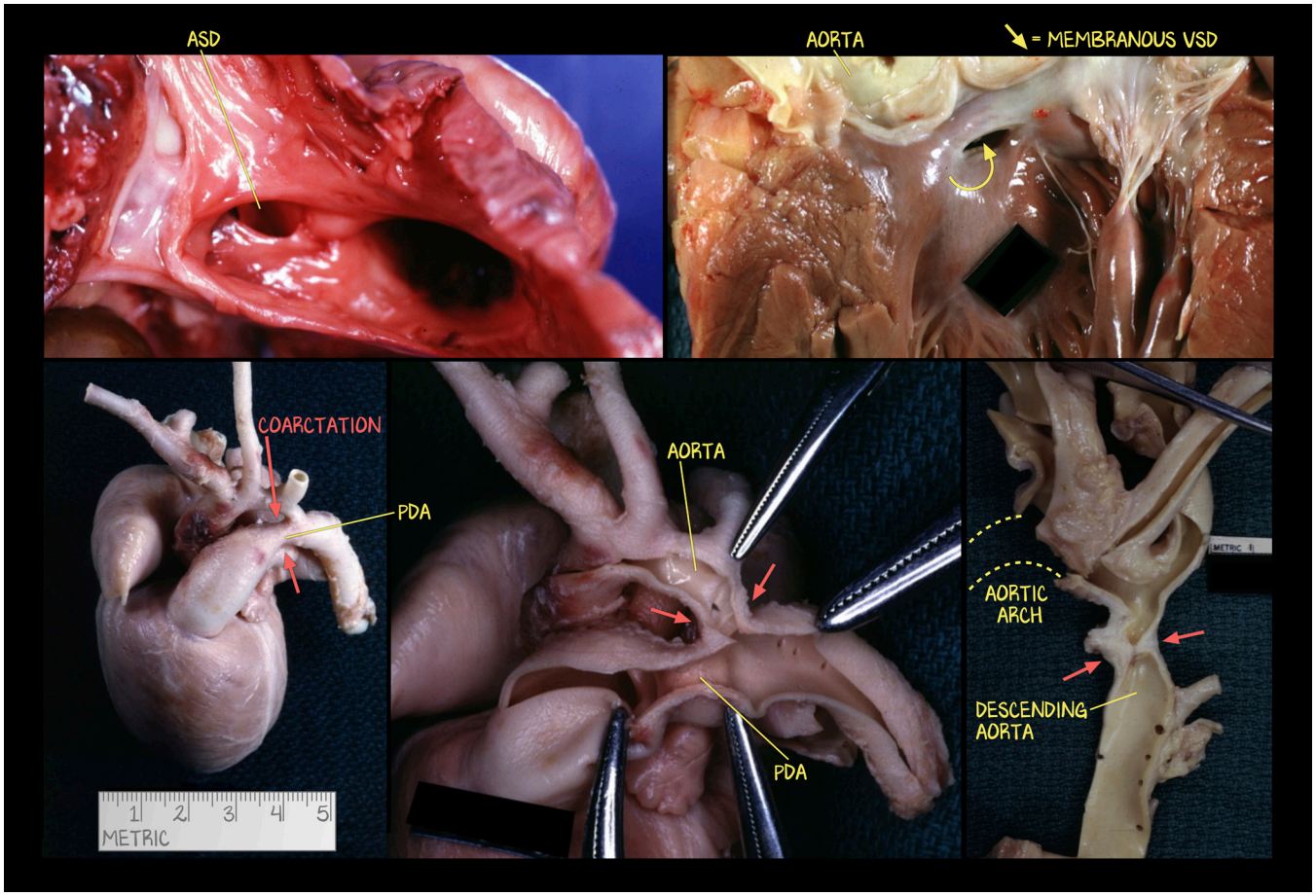

Figure 4.6: Examples of Conditions